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Clinical/Epidemiological Analysis of Congenital Anomalies Associated With Diaphragmatic Hernia

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Several studies have been published on congenital diaphragmatic hernia (CDH), either as an isolated defect or as part of a multiple congenital anomaly (MCA) pattern. Here we present an epidemiological study designed to measure the association between CDH and a group of 17 selected congenital anomalies in an attempt to identify groups of specific defect patterns. This analysis was done using the data from the Spanish Collaborative Study of Congenital Malformations (ECEMC). © 1996 Wiley-Liss, Inc.

KEY WORDS: epidemiology, MCA patterns, diaphragmatic defects, diaphragmatic hernia, developmental field defects, associations

INTRODUCTION

Congenital diaphragmatic defects (CDH) are defects of diaphragm embryogenesis which occur from weeks 3–7 of development, and which cause the organs of the abdominal cavity to herniate into the chest cavity. There are several studies of this anomaly as either an isolated defect or as part of a multiple congenital anomaly (MCA) pattern [Cantrell et al., 1958; David and Illingworth, 1976; Benjamin et al., 1988; Cunniff et al., 1990; Milne et al., 1990; Wenstrom et al., 1991; Siebert et al., 1992; Torfs et al., 1992; Fauza and Wilson, 1994]. Nevertheless, no epidemiological study has yet measured the association between CDH and a group of selected congenital anomalies.

Here we present an analysis of the association between CDH and a group of 17 selected congenital defects in an attempt to identify groups of specific patterns of defects. This analysis used data from the Spanish Collaborative Study of Congenital Malformations (ECEMC).

MATERIALS AND METHODS

The study was based on 24,005 live- and stillborn malformed infants with major and/or mild malformations and some minor anomalies detected during the first 3 days of life. The malformed infants were identified through the ECEMC. The methodology of this hospital-based case-control study and surveillance system is aimed not only at surveillance of congenital anomalies, but also at investigating their characteristics, clustering, and causes. The methodology has been published previously [Martínez-Frías et al., 1991; Martínez-Frías, 1994; Martínez-Frías and Urioste, 1994].

As previously reported [Martínez-Frías, 1994], the ECEMC coding system has different levels for identifying clinical patterns. This allows retrieval, as isolated cases, of those infants with only one defect, including its sequence. For instance, we have considered as isolated CDH those infants with only diaphragmatic hernia, lung hypoplasia, dextrocardia, and malrotation of gut.

Here we analyze the association between CDH and the following group of selected congenital anomalies as a hypothesis generation: cardiovascular defects, renal anomalies, upper limb deficiencies, cleft lip and/or cleft palate, omphalocele, urinary tract anomaly, lower-limb deficiencies, spina bifida, imperforate anus, Meckel diverticulum, microphthalmia, esophageal atresia, polysplenia, holoprosencephaly, nail hypoplasia, microcephaly, and vertebral and/or rib defects (Jarcho-Levin phenotype or vertebral fusion, or hemivertebrae or agenesis/hypoplasia of vertebrae, or absence of ribs). These anomalies were selected because some are suspected of being preferentially associated with CDH, and others because they are the most frequent among the group of infants with CDH, in order to generate new hypotheses.

To analyze the data, we used the method described by Prieto and Martínez-Frías [1996]. As we study only malformed infants, the method requires the cases be distributed by presence or absence of CDH as it is shown in Table I.

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TABLE I. Example of the Distribution of Malformed Infants*

Study defects[a]	With diaphragmatic hernia, with or without other defects	Without diaphragmatic hernia, but with other defects	Total
A	281[a]	20,849 minus isolated A[b]	21,130
B	281[a]	20,849 minus isolated B[b]	21,130
Total	281	20,849	21,130

*A, B, different study defects. a = Number of infants with each study defect *with* CDH with or without other congenital defects. b = Number of infants with each study defect *without* CDH but *with* other congenital defects.

The association of CDH with each one of the selected congenital defects was studied by counting the number of infants with each one of the selected defects in the two columns of table I. For instance, to analyze the association of spina bifida (SB) with CDH, one calculates the proportion of infants with SB among the 281 infants with CDH, and the proportion of cases with SB among the total of 20,431 malformed children without CDH once we excluded the 418 cases of isolated SB (i.e., 20,849 minus the 418 isolated SB cases). The quotient of these two proportions gives the times the proportion of infants with SB is higher in children with CDH (with or without other congenital defects), than in infants without CDH but with other congenital defects. If the result of this analysis is not statistically significant, then we need to do the study in the other direction. That is, the quotient between the proportion of infants with CDH among those with SB, and the proportion of infants with CDH among those malformed infants without SB. This method, like that proposed by Khoury et al. [1990], controls the generalized and nonspecific tendency for defects to cluster among themselves.

RESULTS

Table II presents the study population by clinical presentation. Among malformed infants with isolated anomalies, 1.08% had CDH; this defect was observed in 2.68% of infants with MCA patterns, and in 0.56% of syndromal cases. The total of malformed infants with CDH is 1.24%.

Using the total of 21,130 malformed infants who do not have an identified syndrome or a well-defined entity such as limb-body wall complex with sirenomelia, Table III presents the frequency of each one of the selected congenital anomalies among infants with CDH, and among malformed infants without CDH excluding each isolated defect. Dividing the percentage for patients with each group of selected congenital defects observed among infants with CDH, by the corresponding percentages observed in the reference group of children without CDH (relative frequency, RF), gives the times the proportion of infants with each of the study defects is higher in children with CDH (with or without other congenital defects), than in infants with other congenital defects. This quotient controls the generalized and nonspecific tendency for defects to cluster among themselves. The Fisher test gives the *P* value. As Table III indicates, in all but urinary tract anomalies, microphthalmia, holoprosencephaly, nail hypoplasia, and microcephaly, the results are statistically significant, showing a greater association with CDH than with other congenital defects.

The association of the selected congenital defects with CDH has also been analyzed in infants with known syndromes and defined entities with and without CDH (Table IV). Although the value for RF indicates that all of the selected anomalies are more frequent among infants with those syndromes that include CDH, the RF values for upper-limb deficiencies, omphalocele, and esophageal atresia do not reach statistical significance, perhaps due to the sample size. Table V indicates the types of syndromes and entities with CDH included in Table IV, and types of suspected syndromes (not confirmed because of lack of information) in infants with CDH as part of the MCA patterns that are included in Table III.

Table VI, which has the same structure as Table III, analyzes all malformed children without syndromes, but also excluding those whose clinical patterns strongly suggest they might have a syndrome which was unconfirmed because of a lack of information. The results show that cleft lip and/or cleft palate, urinary tract anomalies, imperforate anus, microphthalmia, esophageal atresia, holoprosencephaly, nail hypoplasia,

TABLE II. Study Population

Clinical presentation	With diaphragmatic hernia N	With diaphragmatic hernia %	Without diaphragmatic hernia (N)	Total
Isolated	194	1.08	17,687	17,881
MCA patterns	87	2.68	3,162	3,249
Total	281	1.33	20,849	21,130
Syndromic	16	0.56	2,859	2,875
Total	297	1.24	23,708	24,005

TABLE III. Distribution of Selected Congenital Defects Among Cases With and Without Diaphragmatic Hernia, Excluding Syndromes

Anomalies	With diaphragmatic hernia N	%	Without diaphragmatic hernia N	%	Total[a]	RF[b]	P
Cardiovascular	29	10.32	714	3.48	20,494	2.97	0.0000000
Renal	18	6.41	324	1.58	20,531	4.06	0.000001
Upper-limb deficiencies	9	3.20	176	0.86	20,533	3.72	0.00095
Cleft lip and/or cleft palate	12	4.27	241	1.21	19,911	3.53	0.0002
Omphalocele	9	3.20	54	0.26	20,777	12.31	0.0000001
Urinary tract anomalies	6	2.14	200	0.97	20,649	2.21	NS
Lower-limb deficiencies	6	2.14	96	0.46	20,691	4.65	0.003
Spina bifida	5	1.78	94	0.46	20,431	3.87	0.01
Imperforate anus	5	1.78	106	0.51	20,734	3.49	0.02
Meckel diverticulum	5	1.78	9	0.04	20,844	44.50	0.0000007
Microphthalmia	4	1.42	115	0.55	20,829	2.58	NS
Esophageal atresia	4	1.42	80	0.39	20,723	3.64	0.03
Polysplenia	4	1.42	18	0.09	20,849	15.78	0.0002
Holoprosencephaly	3	1.07	118	0.57	20,842	1.88	NS
Nail hypoplasia	2	0.71	60	0.29	20,835	2.45	NS
Microcephaly	3	1.07	129	0.62	20,788	1.73	NS
Vertebral and/or rib defects	9	3.20	152	0.73	20,838	4.38	0.0003
Total	281	100.—	20,849				

[a]Total excluding isolated cases of each group of studied anomalies. Thus, the differences with the total of 20,849 correspond to the isolated cases in each study group.
[b]RF, relative frequency.

and microcephaly are not preferentially associated with CDH, while the rest of the selected congenital anomalies do associate preferentially with CDH. But as the analysis is influenced by the frequency in which each defect is associated with other defects, we need to do the analysis in the other direction, in those defects with nonsignificant results. This analysis is presented in Table VII. Only urinary tract anomalies were preferentially associated with CDH. The differences between Tables VI and VII from Table III essentially reflect the cases with patterns of defects compatible with Fryns syndrome and trisomy 13 and 18, where chromosomal analysis was not performed. In fact, the differences from Table III were for cleft lip and/or cleft palate, imperforate anus, and esophageal atresia, defects that are strongly associated with those syndromes.

TABLE IV. Distribution of Different Congenital Defects Among Syndromes With and Without Diaphragmatic Hernia

Anomalies	Syndromes: With diaphragmatic hernia N	%	Without diaphragmatic hernia N	%	RF[a]	P
Cardiovascular	8	50.—	384	13.43	3.72	0.0005
Renal	7	43.75	123	4.30	10.17	0.000003
Upper-limb deficiencies	2	12.50	95	3.32	3.77	NS
Cleft lip and/or cleft palate	5	31.25	131	4.58	6.82	0.0006
Omphalocele	1	6.25	32	1.12	5.58	NS
Urinary tract anomalies	4	25.—	51	1.78	14.04	0.0002
Lower-limb deficiencies	2	12.50	66	2.31	5.41	0.05
Spina bifida	0		26	0.91		
Imperforate anus	0		20	0.70		
Meckel diverticulum	1	6.25	9	0.31	20.16	0.05
Microphthalmia	5	31.25	71	2.48	12.60	0.00004
Esophageal atresia	1	6.25	29	1.01	6.19	NS
Polysplenia	2	12.50	7	0.24	52.08	0.001
Holoprosencephaly	3	18.75	40	1.40	13.39	0.002
Nail hypoplasia	6	37.50	72	2.52	14.88	0.000002
Microcephaly	3	18.75	76	2.66	7.05	0.009
Vertebral and/or rib defects	4	25.—	68	2.38	10.50	0.0005
Total	16	100.—	2,859	100.—		

[a]RF, relative frequency.

TABLE V. Type of Syndromes and Entities, and Cases With a Suspected Syndrome With Diaphragmatic Hernia

	With diaphragmatic hernia	
	N	%
Recognized syndromes		
Trisomy 13	3	18.75
Trisomy 18	8	50.—
Structural chromosomal anomalies	2	12.50
Fryns syndrome	2	12.50
Limb-body wall complex and sirenomelia	1	6.25
Total	16	100.—
Suspected syndromes		
Trisomy 13	3	12.50
Trisomy 18	6	25.—
Trisomy 21	1	4.17
Fryns syndrome	13	54.17
Marfan syndrome	1	4.17
Total	24	100.—

DISCUSSION

This analysis, aimed at identifying possible specific defect patterns which include CDH, shows that some congenital defects are preferentially associated with CDH. In fact, most of them have been previously suspected of being associated with CDH. Fitch et al. [1987] observed that the malformations most frequently associated with CDH involve the heart and the central nervous system. Nevertheless, when cases with well-identified syndromes, and those with a strong clinical suspicion of having a syndrome, were separated from the total group of malformed infants, the anomalies most frequently associated with CDH in infants with *unknown* MCA patterns (Table VI) could be secondary, such as omphalocele, or those which occur during blastogenesis in the primary developmental field [Opitz, 1993], such as polysplenia. The observed significant association with Meckel diverticulum could well be due to an identification bias, since CDH is usually lethal, and autopsy reports are more usually available. Consequently, Meckel diverticulum could be more frequently identified in infants with CDH who died.

Omphalocele was previously observed in infants with CDH [Carmi et al., 1990; Gershoni-Baruch et al., 1990; Milne et al., 1990], and in an epidemiologic study (Martínez-Frías et al., submitted), we have suggested that CDH and omphalocele may be part of the same "problem" (sequence?). Polysplenia was observed by us [Martínez-Frías et al., 1995] as preferentially associated with CDH as a primary developmental field defect (DFD) of alteration of laterality. Renal and urinary tract anomalies, lower-limb deficiencies, and vertebral/rib defects have also been identified in a previous study [Martínez-Frías et al., 1994] as part of the association of spondylocostal dysostosis (in their different degrees of severity) with caudal dysgenesis, CDH, and also spina bifida.

Finally, the association between CDH and upper-limb deficiencies was first described by McCredie and Reid [1978] in 4 unrelated patients, and more recently by Lerone et al. [1992] in 1 child. On the basis of a common pathogenesis, these authors suggested that the association of diaphragmatic defects and upper-limb deficiencies is not coincidental. This preferential association has been demonstrated epidemiologically

TABLE VI. Distribution of Different Congenital Defects Among Cases With and Without Diaphragmatic Hernia, Excluding Syndromes and Cases With a Suspected Syndrome

	Infants with MCA patterns of unknown cause						
	With diaphragmatic hernia		Without diaphragmatic hernia				
Anomalies	N	%	N	%	Total[a]	RF[b]	*P*
Cardiovascular	19	7.39	640	3.18	20,132	2.32	0.0001
Renal	10	3.89	286	1.42	20,169	2.74	0.004
Upper-limb deficiencies	7	2.72	143	0.71	20,171	3.83	0.003
Cleft lip and/or cleft palate	3	1.17	184	0.94	19,549	1.24	NS
Omphalocele	8	3.11	39	0.19	20,415	16.37	0.0000001
Urinary tract anomalies	5	1.95	181	0.89	20,277	2.19	NS
Lower-limb deficiencies	5	1.95	77	0.38	20,329	5.13	0.004
Spina bifida	4	1.56	77	0.38	20,069	4.11	0.02
Imperforate anus	2	0.78	93	0.46	20,372	1.70	NS
Meckel diverticulum	3	1.17	6	0.03	20,482	39.—	0.0001
Microphthalmia	1	0.39	71	0.35	20,467	1.11	NS
Esophageal atresia	1	0.39	69	0.34	20,361	1.15	NS
Polysplenia	4	1.56	14	0.07	20,487	22.29	0.00006
Holoprosencephaly	1	0.39	88	0.43	20,480	0.91	NS
Nail hypoplasia	1	0.39	40	0.20	20,473	1.95	NS
Microcephaly	2	0.78	86	0.42	20,426	1.86	NS
Vertebral and/or rib defects	9	3.50	128	0.63	20,476	5.56	0.00005
Total	257	100.—	20,487				

[a]Total excluding isolated cases in each group of studied anomalies.
[b]RF, relative frequency.

TABLE VII. Analysis of Proportion of Cases With CDH Among Cases With and Without Each of the Following Studied Defects*

	CDH			
	n/N	%	RF	P
With cleft lip and/or cleft palate	2/1,123	0.18	0.6	NS
Without cleft lip and/or cleft palate	59/19,424	0.30		
With urinary tract anomalies	5/397	1.26	4.5	0.007
Without urinary tract anomalies	57/20,150	0.28		
With imperforate anus	2/207	0.97	3.34	NS
Without imperforate anus	60/20,340	0.29		
With microphthalmia	1/91	1.10	3.67	NS
Without microphthalmia	61/20,456	0.30		
With esophageal atresia	1/196	0.51	1.7	NS
Without esophageal atresia	61/20,351	0.30		
With holoprosencephaly	1/95	1.05	3.5	NS
Without holoprosencephaly	61/20,452	0.30		
With nail hypoplasia	1/55	1.82	6.01	NS
Without nail hypoplasia	61/20,494	0.30		
With microcephaly	2/148	1.35	4.66	NS
Without microcephaly	60/20,399	0.29		

*n, number of infants with CDH with or without each study defect, but with other defects; N, total of malformed infants, excluding syndromes and cases with a suspected syndrome, minus isolated CDH; RF, relative frequency; NS, statistically nonsignificant.

TABLE VIII. Association of Different Studied Congenital Defects With Diaphragmatic Hernia in Infants With Syndromes and With MCA Patterns

	Infants with	
Anomalies	Syndromes	MCA patterns
Cardiovascular	+	+
Renal	+	+
Lower-limb deficiencies	+	+
Polysplenia	+	+
Vertebral and/or rib defects	+	+
Urinary tract anomalies	+	+
Cleft lip and/or cleft palate	+	−
Microphthalmia	+	−
Holoprosencephaly	+	−
Nail hypoplasia	+	−
Microcephaly	+	−
Upper-limb deficiencies	−	+
Omphalocele	−	+
Spina bifida	−	+
Imperforate anus	−	−
Esophageal atresia	−	−

by Martínez-Frías [1996], and we suggest that it is a polytopic primary developmental field defect.

In conclusion, most of the studied defects are associated with CDH in syndromes (Table VIII); but 7 out of 17 (cleft lip and/or cleft palate, imperforate anus, microphthalmia, esophageal atresia, holoprosencephaly, nail hypoplasia, and microcephaly) are not preferentially associated with CDH in infants with *unknown* MCA patterns. Thus, their association with CDH in the same child could be considered as part of a general and nonspecific tendency for defects to associate among themselves once chromosomal abnormalities or other well-known syndromes have been excluded. The other 10 studied defects are part of four different specific patterns of preferential associations with CDH: 1) CDH ± caudal dysgenesis ± spondylocostal dysostosis ± spina bifida; 2) CDH + omphalocele; 3) CDH + upper-limb deficiencies, as a polytopic primary developmental field defect; and 4) CDH + polysplenia as a primary developmental field defect of alteration of laterality.

As we have shown here, the analysis of possible defect associations is more powerful if the cases are separated by cause, and if the different clinical groups to be studied are identified before beginning the analysis.

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